Somatic mutations that contribute to clonal hematopoiesis and cardiovascular disease risk: New mechanisms, new pharmacological targets

Kenneth Walsh

University of Virginia, Center for Hematovascular Biology and Berne Cardiovascular Research Center, USA

There has long been debate that the traditional, modifiable risk factors (hyperlipidemia, hypertension, diabetes and smoking), all established more than 50 years ago, are incompletely predictive of cardiovascular disease (CVD). Furthermore, we have a poor understanding of how aging, the major CVD risk factor, promotes disease progression. Somatic DNA mutations accumulate with age in many tissues, leading to genomic mosaicism. However, the causal role of genomic mosaicism in the diseases of the elderly other than cancer is relatively unexplored. Large exome sequencing studies in humans have shown that aging is associated with an increased frequency of somatic mutations in the hematopoietic system that provide a competitive growth advantage to the mutant cell and therefore allow its clonal expansion (i.e. clonal hematopoiesis). Unexpectedly, these somatic mutations have been found to be associated with greater risk of coronary heart disease and stroke, suggesting a previously unrecognized link between somatic mutations in the hematopoietic system and CVD. One of the genes that is frequently mutated in clonal hematopoiesis is the epigenetic regulator Tet2. Using Tet2 as a test case, we explored whether the expansion of mutant hematopoietic cells promotes atherosclerosis and heart failure in experimental models. The findings of these studies support the concept that clonal hematopoiesis, due to somatic mutations, represents a new mechanism of CVD that shares features with hematologic malignancy. Further research in the area of hematovascular biology could provide a mechanistic framework for the development of personalized medicines for CVD that are tailored for individuals that carry specific somatic mutations in their hematopoietic cells.